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- (54) **GENETIC MARKERS FOR EFFICACY OF ILOPERIDONE IN THE TREATMENT OF PSYCHOTIC SYMPTOMS**
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None
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- (56) **References Cited**

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(57) ABSTRACT

Methods for predicting whether iloperidone will be efficacious in treating a psychotic symptom in an individual, based on the individual's genotype at one or more single nucleotide polymorphism (SNP) loci are described, as are methods for treating an individual based on such prediction.

13 Claims, No Drawings

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GENETIC MARKERS FOR EFFICACY OF ILOPERIDONE IN THE TREATMENT OF PSYCHOTIC SYMPTOMS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/939,033, filed 18 May 2007, which is hereby incorporated herein.

BACKGROUND OF THE INVENTION

1. Technical Field

The invention relates generally to the treatment of psychotic symptoms, and more particularly, to predicting whether iloperidone, an iloperidone metabolite, or pharmaceutically-acceptable salts thereof will be efficacious in treating an individual's psychotic symptoms, based on the individual's genotype at one or more single nucleotide polymorphism (SNP) loci.

2. Background Art

Schizophrenia is a psychotic disorder affecting approximately 1% of the US population. It is characterized by the presence of positive symptoms (e.g., hallucinations and delusions) and negative symptoms (e.g., blunted affect and social withdrawal), as well as impairment of cognitive functions. There is much evidence that schizophrenia may not be caused by a single major gene, but rather by several interacting susceptibility loci.

The nature and severity of an individual's schizophrenia may be measured using a number of scales, the most widely used being the Positive and Negative Syndrome Scale (PANSS). A number of PANSS subscales may also be used, such as the PANSS general psychopathology subscale (PANSS-GP), the PANSS positive symptom subscale (PANSS-P), and the PANSS negative symptom subscale (PANSS-N). The PANSS total score (PANSS-T) is comprised of all PANSS subscales.

Perhaps due to the heterogeneity of the underlying disease process, the etiology of schizophrenia has not been identified. Genetic factors are expected to play a role in the response to drug treatment. Several studies have shown that a polymorphism in the serotonin 5-HT_{2A} receptor may be associated with the efficacy of clozapine and risperidone.

Iloperidone is classified as an atypical antipsychotic, most commonly characterized by their relatively low affinity for dopamine D₂ receptors and high affinity for serotonin 5-HT₂ receptors. Data stemming from the iloperidone clinical program indicate that the response to iloperidone is variable, as is the case with all marketed antipsychotics.

SUMMARY OF THE INVENTION

The invention provides a method for predicting whether iloperidone is likely to be efficacious in treating psychotic symptoms, such as hallucinations and delusions, in psychiatric disorders, including schizophrenia, schizoaffective disorders, bipolar I, bipolar II, and major depression with psychiatric features, in an individual, based on the individual's genotype at one or more single nucleotide polymorphism (SNP) loci, as well as a related method for treating an individual based on such prediction.

A first aspect of the invention provides a method of predicting the efficacy of using iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite in the treatment of at least

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one psychotic symptom in an individual, the method comprising: determining the individual's genotype at least one single nucleotide polymorphism (SNP) locus selected from a group consisting of: SNP_A-2048427, SNP_A-2283283, SNP_A-1973093, SNP_A-2284243, SNP_A-2274533, SNP_A-2076797, SNP_A-4212785, SNP_A-4230979, SNP_A-2007721, SNP_A-2170121, SNP_A-2103099, SNP_A-1975928, SNP_A-4258279, SNP_A-1934663, SNP_A-2120958, SNP_A-4204396, SNP_A-4256833, SNP_A-1860353, SNP_A-2070454, SNP_A-2044214, SNP_A-1987915, and SNP_A-1819750; and, in the case that the individual's genotype at the at least one SNP locus is associated with greater iloperidone efficacy, predicting that treating the individual with iloperidone will be efficacious.

A second aspect of the invention provides a method of treating a psychotic symptom in an individual, comprising: determining the individual's genotype at least one single nucleotide polymorphism (SNP) locus selected from a group consisting of: SNP_A-2048427, SNP_A-2283283, SNP_A-1973093, SNP_A-2284243, SNP_A-2274533, SNP_A-2076797, SNP_A-4212785, SNP_A-4230979, SNP_A-2007721, SNP_A-2170121, SNP_A-2103099, SNP_A-1975928, SNP_A-4258279, SNP_A-1934663, SNP_A-2120958, SNP_A-4204396, SNP_A-4256833, SNP_A-1860353, SNP_A-2070454, SNP_A-2044214, SNP_A-1987915, and SNP_A-1819750; and in the case that the individual's genotype at the at least one SNP locus is associated with greater iloperidone efficacy, administering to the individual a quantity of iloperidone.

A third aspect of the invention provides a method of predicting the efficacy of using iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite in the treatment of at least one psychotic symptom in an individual, the method comprising: characterizing an expression product of a gene associated with at least one single nucleotide polymorphism (SNP) locus selected from a group consisting of: SNP_A-2048427, SNP_A-2283283, SNP_A-1973093, SNP_A-2284243, SNP_A-2274533, SNP_A-2076797, SNP_A-4212785, SNP_A-4230979, SNP_A-2007721, SNP_A-2170121, SNP_A-2103099, SNP_A-1975928, SNP_A-4258279, SNP_A-1934663, SNP_A-2120958, SNP_A-4204396, SNP_A-4256833, SNP_A-1860353, SNP_A-2070454, SNP_A-2044214, SNP_A-1987915, and SNP_A-1819750; and, in the case that the expression product is associated with greater iloperidone efficacy, predicting that treating the individual with iloperidone will be efficacious.

A fourth aspect of the invention provides a method of treating a psychotic symptom in an individual, comprising: characterizing an expression product of a gene associated with at least one single nucleotide polymorphism (SNP) locus selected from a group consisting of: SNP_A-2048427, SNP_A-2283283, SNP_A-1973093, SNP_A-2284243, SNP_A-2274533, SNP_A-2076797, SNP_A-4212785, SNP_A-4230979, SNP_A-2007721, SNP_A-2170121, SNP_A-2103099, SNP_A-1975928, SNP_A-4258279, SNP_A-1934663, SNP_A-2120958, SNP_A-4204396, SNP_A-4256833, SNP_A-1860353, SNP_A-2070454, SNP_A-2044214, SNP_A-1987915, and SNP_A-1819750; and, in the case that the expression product is associated with greater iloperidone efficacy, administering to the individual a quantity of iloperidone.

DETAILED DESCRIPTION

Earlier studies investigated an association between a polymorphism in the CNTF gene and iloperidone efficacy as well

as associations between CYP2D6 and KCNQ1 genotypes and changes in QT interval following the administration of iloperidone. The present study involved the genotyping of DNA samples collected from 426 individuals diagnosed with schizophrenia in an attempt to identify additional SNPs associated with iloperidone efficacy.

Each sample was genotyped at more than 500,000 SNP loci using the GeneChip® Human Mapping 500K Array Set (Affymetrix, Santa Clara, Calif.) and using assays developed in-house.

Approximately half of the participants in the study were administered 24 mg/day of iloperidone, b.i.d., for 28 days. About 25% of the patients were administered ziprasidone. The remaining participants were administered a placebo.

Three analyses of the PANSS-T were conducted. 1) A two-step approach where samples were randomly split into 2 groups of iloperidone-treated patients used to discover SNPs associated with changed in PANSS-T (Discovery phase) and

a second group to confirm the 100 most significant SNPs (Confirmatory phase). 2) A one-step approach using the Last Observation Carried Forward (LOCF) PANSS-T data of all iloperidone-treated patients. For each SNP, the most parsimonious genetic model (e.g., homozygous for one allele v. all other genotypes [i.e., AA v. AB and BB], heterozygous v. homozygous [i.e., AB v. AA and BB]) was established with respect to iloperidone efficacy using a one-way analysis of variance (ANOVA). 3) A Mixed-effects Model Repeated Measures (MMRM) analysis was subsequently conducted using the best genetic model of each SNP in the MMRM model. MMRM analyses were also conducted with the PANSS subscales PANSS-P, PANSS-N, and PANSS-GP.

The SNPs with a statistically significant association in all 3 analyses of PANSS-T, as well as the best of each analysis were considered significant findings and are listed below in Table 1. Results for each of these SNPs with the PANSS-T scales and with the three subscales PANSS-P, PANSS-N, and PANSS-GP are shown in Tables 2, 3, 4, and 5, respectively.

TABLE 1

SNPs associated with efficacy in iloperidone-treated patients								
SNP ¹	dbSNP ¹	Gene ²	Chr.	Cyto	Position ³	allele A ⁴	allele B ⁴	Genotype ⁵
SNP_A-1819750	rs2902346	CREG1	1	q24.2	165793447	A	G	nonAB
SNP_A-1860353	rs17105331	RAP1B	12	q15	67030804	A	G	AA
SNP_A-1934663	rs6565249		16	p11.2	31476343	A	G	nonBB
SNP_A-1973093	rs875326	KIAA0040	1	q25.1	173556022	A	G	nonAB
SNP_A-1975928	rs16892475	SLC2A9	4	p16.1	9649371	A	C	nonBB
SNP_A-1987915	rs1931990	GPR126	6	q24.1	142638813	A	G	BB
SNP_A-2007721	rs1473470	LOC58486	11	p15.3	11003055	C	G	AB
SNP_A-2044214	rs7939190	HNT	11	q25	131362795	A	G	nonAB
SNP_A-2048427	rs11851892	NPAS3	14	q13.1	32921165	A	G	nonBB
SNP_A-2070454	rs11744669	NKX2-5	5	q35.2	172657942	A	G	BB
SNP_A-2076797	rs4528226	NUDT9P1	10	q23.31	92822226	G	T	AB
SNP_A-2103099	rs10039523	HTR1A	5	q12.1	62457846	A	G	nonAB
SNP_A-2120958	rs6669798		1	p33	48160175	C	T	nonBB
SNP_A-2170121	rs17260228	C6	5	p13.1	41204861	C	T	AB
SNP_A-2274533	rs7837682	LZTS1	8	p21.3	21329990	A	G	AA
SNP_A-2283283	rs9643483	XKR4	8	q12.1	55960228	G	T	nonAA
SNP_A-2284243	rs2513265	GRIA4	11	q22.3	104929005	A	T	nonBB
SNP_A-4204396	rs7206381	CDH13	16	q23.3	81620805	C	T	nonBB
SNP_A-4212785	rs17155176	PPP1R3B	8	p23.1	8973511	C	T	nonAA
SNP_A-4230979	rs13019052	ASB3	2	p16.2	52901041	C	G	BB
SNP_A-4256833	rs4401068	MLCK	16	q11.2	45354669	A	G	nonAB
SNP_A-4258279	rs7946885	RRM1	11	p15.4	4120756	A	G	nonAB

¹SNPs are identified by their Affymetrix SNP nomenclature (SNP_A-) and their unique dbSNP number (<http://www.ncbi.nlm.nih.gov/projects/SNP/>) dbSNP version 126, May 2006.

²The gene name corresponds to the NCBI official symbol of the gene associated with the SNP as annotated by Affymetrix. Note that when a SNP is associated with more than one gene, the name of only the first gene in the annotation is listed. The SNP could be within or nearby the gene listed, or another gene in the same chromosomal region.

³The address of each SNP in the genome is indicated by its chromosome (Chr.), cytoband (Cyto), location and the physical position as listed in the NCBI Build 36.1, March 2006 (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp>).

⁴The nucleotides corresponding to the A and B alleles are listed as defined by Affymetrix. Their relation of the + and - strands is available at the NCBI dbSNP web site listed above.

⁵The genotype class associated with better iloperidone response is shown using the Affymetrix allele nomenclature.

TABLE 2

SNPs associated with PANSS-T score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-1934663		5.42404E-05	0.072815255	A_A	15	-18.67	3.20
		5.42404E-05	0.072815255	A_B	58	-18.34	4.25
		5.42404E-05	0.072815255	B_B*	115	-8.39	4.71
		5.42404E-05	0.072815255	nonBB**	73	-18.40	4.04
SNP_A-1973093	KIAA0040	2.11212E-05	0.000607322	A_A	25	-14.99	4.27
		2.11212E-05	0.000607322	A_B*	76	-6.21	4.51
		2.11212E-05	0.000607322	B_B	105	-16.73	4.33
		2.11212E-05	0.000607322	nonAB**	130	-16.39	4.35
SNP_A-2070454	NKX2-5	0.000646006	0.000122264	A_A	44	-9.88	5.04
		0.000646006	0.000122264	A_B	94	-10.39	4.07
		0.000646006	0.000122264	B_B**	61	-18.31	4.43
		0.000646006	0.000122264	nonBB*	138	-10.23	4.39

TABLE 2-continued

SNPs associated with PANSS-T score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-2076797	NUDT9P1	7.78445E-07	0.015918222	A_A	57	-7.14	4.10
		7.78445E-07	0.015918222	A_B**	99	-18.73	3.99
		7.78445E-07	0.015918222	B_B	52	-6.04	4.45
		7.78445E-07	0.015918222	nonAB*	109	-6.61	4.29
SNP_A-2103099	HTR1A	3.13417E-05	5.86485E-07	A_A	38	-17.43	4.64
		3.13417E-05	5.86485E-07	A_B*	105	-8.31	4.34
		3.13417E-05	5.86485E-07	B_B	65	-16.12	4.21
		3.13417E-05	5.86485E-07	nonAB**	103	-16.60	4.40
SNP_A-2120958		7.60281E-05	0.00188507	A_A	116	-13.95	4.28
		7.60281E-05	0.00188507	A_B	77	-13.71	4.67
		7.60281E-05	0.00188507	B_B*	17	2.48	5.38
		7.60281E-05	0.00188507	nonBB**	193	-13.85	4.43
SNP_A-2170121	C6	1.69136E-05	0.000229991	A_A	137	-8.94	4.27
		1.69136E-05	0.000229991	A_B**	53	-21.93	3.86
		1.69136E-05	0.000229991	B_B	14	-11.50	3.58
		1.69136E-05	0.000229991	nonAB*	151	-9.17	4.27
SNP_A-2283283	XKR4	0.000172366	0.000425434	A_A*	47	-3.30	3.93
		0.000172366	0.000425434	A_B	96	-14.57	4.35
		0.000172366	0.000425434	B_B	67	-15.66	4.28
		0.000172366	0.000425434	nonAA**	163	-15.02	4.34
SNP_A-4256833	MLCK	0.000353368	0.002609391	A_A	9	-15.19	3.02
		0.000353368	0.002609391	A_B*	64	-6.20	5.21
		0.000353368	0.002609391	B_B	137	-15.15	4.23
		0.000353368	0.002609391	nonAB**	146	-15.15	4.15
SNP_A-4258279	RRM1	4.67654E-05	0.005619516	A_A	2	-13.42	3.08
		4.67654E-05	0.005619516	A_B*	45	-2.55	4.42
		4.67654E-05	0.005619516	B_B	160	-14.72	4.15
		4.67654E-05	0.005619516	nonAB**	162	-14.70	4.13
SNP_A-1819750	CREG1	0.017284377	0.100418357	A_A	22	-18.13	4.58
		0.017284377	0.100418357	A_B*	119	-10.74	4.70
		0.017284377	0.100418357	B_B	46	-16.05	4.74
		0.017284377	0.100418357	nonAB**	68	-16.72	4.76
SNP_A-1860353	RAP1B	0.000625325	0.005405007	A_A**	5	-37.40	4.03
		0.000625325	0.005405007	A_B	35	-11.79	4.23
		0.000625325	0.005405007	B_B	169	-11.84	4.03
		0.000625325	0.005405007	nonAA*	204	-11.83	4.06
SNP_A-1975928	SLC2A9	4.61282E-05	0.003653312	A_A	150	-13.09	4.57
		4.61282E-05	0.003653312	A_B	48	-13.17	4.05
		4.61282E-05	0.003653312	B_B*	6	16.38	6.49
		4.61282E-05	0.003653312	nonBB**	198	-13.11	4.44
SNP_A-1987915	GPR126	0.001249144	0.029776522	A_A	27	-9.87	5.11
		0.001249144	0.029776522	A_B	97	-9.61	4.60
		0.001249144	0.029776522	B_B**	85	-17.29	4.25
		0.001249144	0.029776522	nonBB*	124	-9.67	4.69
SNP_A-2007721	LOC58486	1.0792E-05	0.000560557	A_A	1	-4.55	
		1.0792E-05	0.000560557	A_B**	48	-22.64	4.50
		1.0792E-05	0.000560557	B_B	147	-9.55	3.93
		1.0792E-05	0.000560557	nonAB*	148	-9.52	3.94
SNP_A-2044214	HNT	0.000944901	0.002995624	A_A	86	-15.71	4.97
		0.000944901	0.002995624	A_B*	78	-7.43	3.87
		0.000944901	0.002995624	B_B	46	-14.43	4.27
		0.000944901	0.002995624	nonAB**	132	-15.26	4.76
SNP_A-2048427	NPAS3	9.30226E-05	0.008990872	A_A	9	-19.94	2.44
		9.30226E-05	0.008990872	A_B	56	-20.15	3.87
		9.30226E-05	0.008990872	B_B*	145	-9.20	4.25
		9.30226E-05	0.008990872	nonBB**	65	-20.12	3.69
SNP_A-2274533	LZTS1	0.000180835	0.00115156	A_A**	116	-15.95	4.23
		0.000180835	0.00115156	A_B	64	-6.04	4.55
		0.000180835	0.00115156	B_B	18	-6.21	3.21
		0.000180835	0.00115156	nonAA*	82	-6.08	4.28
SNP_A-2284243	GRIA4	5.54999E-05	0.001000122	A_A	63	-15.30	4.46
		5.54999E-05	0.001000122	A_B	99	-15.17	4.16
		5.54999E-05	0.001000122	B_B*	48	-3.30	4.11
		5.54999E-05	0.001000122	nonBB**	162	-15.22	4.26
SNP_A-4204396	CDH13	8.05822E-05	0.005999381	A_A	111	-13.72	4.52
		8.05822E-05	0.005999381	A_B	67	-14.04	4.02
		8.05822E-05	0.005999381	B_B*	15	4.89	5.46
		8.05822E-05	0.005999381	nonBB**	178	-13.84	4.33
SNP_A-4212785	PPP1R3B	2.46186E-06	0.002306863	A_A*	4	25.90	3.38
		2.46186E-06	0.002306863	A_B	67	-13.66	4.31
		2.46186E-06	0.002306863	B_B	124	-13.56	4.19
		2.46186E-06	0.002306863	nonAA**	191	-13.60	4.22

TABLE 2-continued

SNPs associated with PANSS-T score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-4230979	ASB3	6.05937E-06	9.86017E-05	A_A	26	-6.70	3.39
		6.05937E-06	9.86017E-05	A_B	98	-8.77	4.59
		6.05937E-06	9.86017E-05	B_B**	85	-18.82	4.25
		6.05937E-06	9.86017E-05	nonBB*	124	-8.34	4.43

¹SNPs are identified by their Affymetrix SNP nomenclature (SNP_A-)

²The gene name corresponds to the NCBI official symbol of the gene associated with the SNP as annotated by Affymetrix. Note that when a SNP is associated with more than one gene, the name of only the first gene in the annotation is listed. The SNP could be within or nearby the gene listed, or another gene in the same chromosomal region.

³p value of the MMRM analysis between the 2 genotype classes associated with lowest * or highest ** response to iloperidone treatment

⁴p value of the MMRM analysis between the iloperidone (Ilo) and placebo (Pbo) groups for the genotype class associated with the better response (**).

⁵The 2 genotypes classes used in the MMRM analyses are indicated with lowest * or highest ** response to iloperidone treatment.

⁶The number of patients (N), the mean of change in PANSS-T (Mean), and the standard deviation of the mean (Std) shown here are derived from the MMRM analysis done within the group of iloperidone-treated patients.

As used herein, “greater iloperidone efficacy” means an improvement in PANSS-T score of at least about 20%. In the current study, this means an improvement of at least 13 points.

The predictive potential of a SNP may be better appreciated when expressed in terms of an Odds Ratio (likelihood that an individual having a genotype associated with greater iloperidone efficacy will experience greater iloperidone efficacy than would an individual not having a genotype associated with greater iloperidone efficacy), Sensitivity (probability that an individual with have a genotype associated with greater iloperidone efficacy, given that he/she experience greater iloperidone efficacy), Specificity (probability that an individual will not have a genotype associated with greater iloperidone efficacy, given that he/she does not experience greater iloperidone efficacy), negative predictive value (probability that an individual will not experience greater iloperidone efficacy, given that he/she does not have a genotype associated with greater iloperidone efficacy), and positive predictive value (probability that an individual will experience greater iloperidone efficacy, given that he/she has a

genotype associated with greater iloperidone efficacy). These values are shown in Table 6 below.

Among the 6 SNPs identified in all 3 analyses of PANSS-T and listed in Table 6, SNP_A-2048427 was the SNP with the highest specificity (79%) and best positive predictive value (62%). The SNPs with the highest sensitivity (87%) were SNP_A-2274533 and SNP_A-2283283. These SNPs also provided the best negative predictive values (75% and 74%, respectively).

Interestingly, the effect of these SNPs on each of the PANSS subscales varied. For example, SNP_A-2076797 exhibited the strongest association in the PANSS-P subscale, SNP_A-2274533 exhibited the strongest association in the PANSS-N subscale, and SNP_A-1973093 exhibited the strongest association in the PANSS-GP subscale. These results are shown below in Tables 3-5 and underscore the value of evaluating several genetic markers when analyzing a clinical phenotype as complex as drug response. In the present case of iloperidone efficacy, it is likely that different markers are more specifically associated with one or a few specific clinical symptoms, which is reflected in the improvement measured in separate subscales.

TABLE 3

SNPs associated with PANSS-P score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-1934663		0.003905021	0.017701441	A_A	15	-5.65	1.43
		0.003905021	0.017701441	A_B	58	-5.78	1.49
		0.003905021	0.017701441	B_B*	115	-3.40	1.71
		0.003905021	0.017701441	nonBB**	73	-5.75	1.47
SNP_A-1973093	KIAA0040	0.00037196	0.000125358	A_A	25	-5.12	1.46
		0.00037196	0.000125358	A_B*	76	-2.58	1.54
		0.00037196	0.000125358	B_B	105	-5.64	1.47
		0.00037196	0.000125358	nonAB**	130	-5.54	1.47
SNP_A-2070454	NKX2-5	0.024690788	0.000399844	A_A	44	-4.04	1.83
		0.024690788	0.000399844	A_B	94	-3.89	1.38
		0.024690788	0.000399844	B_B**	61	-5.75	1.46
		0.024690788	0.000399844	nonBB*	138	-3.94	1.54
SNP_A-2076797	NUDT9P1	1.67719E-07	5.22823E-05	A_A	57	-2.57	1.37
		1.67719E-07	5.22823E-05	A_B**	99	-6.55	1.39
		1.67719E-07	5.22823E-05	B_B	52	-2.27	1.53
		1.67719E-07	5.22823E-05	nonAB*	109	-2.42	1.45
SNP_A-2103099	HTR1A	4.37186E-06	2.53636E-08	A_A	38	-6.05	1.72
		4.37186E-06	2.53636E-08	A_B*	105	-2.88	1.41
		4.37186E-06	2.53636E-08	B_B	65	-5.88	1.47
		4.37186E-06	2.53636E-08	nonAB**	103	-5.95	1.56
SNP_A-2120958		4.54898E-06	1.76898E-05	A_A	116	-4.97	1.48
		4.54898E-06	1.76898E-05	A_B	77	-4.92	1.48
		4.54898E-06	1.76898E-05	B_B*	17	1.49	1.47
		4.54898E-06	1.76898E-05	nonBB**	193	-4.95	1.48

TABLE 3-continued

SNPs associated with PANSS-P score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-2170121	C6	0.00039812	2.77139E-05	A_A	137	-3.49	1.47
		0.00039812	2.77139E-05	A_B**	53	-6.98	1.35
		0.00039812	2.77139E-05	B_B	14	-4.26	1.00
		0.00039812	2.77139E-05	nonAB*	151	-3.56	1.45
SNP_A-2283283	XKR4	0.001976376	8.73988E-06	A_A*	47	-1.85	1.41
		0.001976376	8.73988E-06	A_B	96	-4.92	1.34
		0.001976376	8.73988E-06	B_B	67	-5.41	1.48
		0.001976376	8.73988E-06	nonAA**	163	-5.12	1.42
SNP_A-4256833	MLCK	0.002452989	0.000199725	A_A	9	-4.59	1.17
		0.002452989	0.000199725	A_B*	64	-2.78	1.82
		0.002452989	0.000199725	B_B	137	-5.14	1.37
		0.002452989	0.000199725	nonAB**	146	-5.10	1.36
SNP_A-4258279	RRM1	5.11554E-06	5.0386E-05	A_A	2	-5.01	0.99
		5.11554E-06	5.0386E-05	A_B*	45	-0.85	1.64
		5.11554E-06	5.0386E-05	B_B	160	-5.25	1.43
		5.11554E-06	5.0386E-05	nonAB**	162	-5.24	1.43
SNP_A-1819750	CREG1	0.274067436	0.042539637	A_A	22	-5.31	1.37
		0.274067436	0.042539637	A_B*	119	-4.28	1.48
		0.274067436	0.042539637	B_B	46	-5.02	1.51
		0.274067436	0.042539637	nonAB**	68	-5.11	1.46
SNP_A-1860353	RAP1B	0.041832082	0.04007533	A_A**	5	-9.20	1.41
		0.041832082	0.04007533	A_B	35	-4.42	1.59
		0.041832082	0.04007533	B_B	169	-4.28	1.37
		0.041832082	0.04007533	nonAA*	204	-4.30	1.40
SNP_A-1975928	SLC2A9	1.50144E-06	9.32666E-05	A_A	150	-4.60	1.62
		1.50144E-06	9.32666E-05	A_B	48	-4.79	1.49
		1.50144E-06	9.32666E-05	B_B*	6	6.19	2.08
		1.50144E-06	9.32666E-05	nonBB**	198	-4.65	1.59
SNP_A-1987915	GPR126	0.001751883	0.002962652	A_A	27	-3.53	1.49
		0.001751883	0.002962652	A_B	97	-3.43	1.53
		0.001751883	0.002962652	B_B**	85	-5.95	1.35
		0.001751883	0.002962652	nonBB*	124	-3.45	1.52
SNP_A-2007721	LOC58486	5.7801E-05	0.000580283	A_A	1	-1.70	
		5.7801E-05	0.000580283	A_B**	48	-7.48	1.51
		5.7801E-05	0.000580283	B_B	147	-3.42	1.35
		5.7801E-05	0.000580283	nonAB*	148	-3.41	1.35
SNP_A-2044214	HNT	2.5043E-06	8.84357E-06	A_A	86	-5.77	1.53
		2.5043E-06	8.84357E-06	A_B*	78	-2.08	1.36
		2.5043E-06	8.84357E-06	B_B	46	-5.64	1.37
		2.5043E-06	8.84357E-06	nonAB**	132	-5.73	1.47
SNP_A-2048427	NPAS3	0.004724236	0.002047518	A_A	9	-6.16	0.74
		0.004724236	0.002047518	A_B	56	-6.26	1.35
		0.004724236	0.002047518	B_B*	145	-3.61	1.46
		0.004724236	0.002047518	nonBB**	65	-6.24	1.28
SNP_A-2274533	LZTS1	0.002564762	0.000131854	A_A**	116	-5.34	1.47
		0.002564762	0.000131854	A_B	64	-2.64	1.57
		0.002564762	0.000131854	B_B	18	-2.63	0.95
		0.002564762	0.000131854	nonAA*	82	-2.63	1.45
SNP_A-2284243	GRIA4	0.002257083	0.000446623	A_A	63	-5.09	1.49
		0.002257083	0.000446623	A_B	99	-5.09	1.51
		0.002257083	0.000446623	B_B*	48	-2.11	1.28
		0.002257083	0.000446623	nonBB**	162	-5.09	1.49
SNP_A-4204396	CDH13	8.30622E-06	0.000224593	A_A	111	-4.76	1.60
		8.30622E-06	0.000224593	A_B	67	-4.99	1.31
		8.30622E-06	0.000224593	B_B*	15	1.63	1.90
		8.30622E-06	0.000224593	nonBB**	178	-4.85	1.50
SNP_A-4212785	PPP1R3B	0.000861132	1.17771E-05	A_A*	4	4.95	1.17
		0.000861132	1.17771E-05	A_B	67	-4.78	1.34
		0.000861132	1.17771E-05	B_B	124	-4.70	1.46
		0.000861132	1.17771E-05	nonAA**	191	-4.73	1.42
SNP_A-4230979	ASB3	0.001139814	0.000253507	A_A	26	-2.80	1.12
		0.001139814	0.000253507	A_B	98	-3.63	1.52
		0.001139814	0.000253507	B_B**	85	-5.84	1.51
		0.001139814	0.000253507	nonBB*	124	-3.45	1.48

¹SNPs are identified by their Affymetrix SNP nomenclature (SNP_A-)

²The gene name corresponds to the NCBI official symbol of the gene associated with the SNP as annotated by Affymetrix. Note that when a SNP is associated with more than one gene, the name of only the first gene in the annotation is listed. The SNP could be within or nearby the gene listed, or another gene in the same chromosomal region.

³p value of the MMRM analysis between the 2 genotype classes associated with lowest * or highest ** response to iloperidone treatment.

⁴p value of the MMRM analysis between the iloperidone (Ilo) and placebo (Pbo) groups for the genotype class associated with the better response (**).

⁵The 2 genotypes classes used in the MMRM analyses are indicated as associated with lowest * or highest ** response to iloperidone treatment.

⁶The number of patients (N), the mean of change in PANSS-P (Mean), and the standard deviation of the mean (Std) shown here are derived from the MMRM analysis done within the group of iloperidone-treated patients.

TABLE 4

SNPs associated with PANSS-N score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-1934663		0.002008934	0.418799746	A_A	15	-3.38	1.84
		0.002008934	0.418799746	A_B	58	-3.94	2.10
		0.002008934	0.418799746	B_B*	115	-2.06	1.97
		0.002008934	0.418799746	nonBB**	73	-3.82	2.05
SNP_A-1973093	KIAA0040	0.007114056	0.068955252	A_A	25	-3.32	1.91
		0.007114056	0.068955252	A_B*	76	-1.85	1.96
		0.007114056	0.068955252	B_B	105	-3.46	1.96
		0.007114056	0.068955252	nonAB**	130	-3.43	1.94
SNP_A-2070454	NKX2-5	4.97557E-05	8.03515E-05	A_A	44	-1.86	2.21
		4.97557E-05	8.03515E-05	A_B	94	-2.40	1.98
		4.97557E-05	8.03515E-05	B_B**	61	-4.58	2.02
		4.97557E-05	8.03515E-05	nonBB*	138	-2.23	2.06
SNP_A-2076797	NUDT9P1	0.000463402	0.080014935	A_A	57	-1.75	2.10
		0.000463402	0.080014935	A_B**	99	-4.06	1.89
		0.000463402	0.080014935	B_B	52	-1.62	1.78
		0.000463402	0.080014935	nonAB*	109	-1.69	1.94
SNP_A-2103099	HTR1A	0.000979899	0.000198436	A_A	38	-4.08	1.97
		0.000979899	0.000198436	A_B*	105	-2.09	1.99
		0.000979899	0.000198436	B_B	65	-3.40	1.85
		0.000979899	0.000198436	nonAB**	103	-3.65	1.91
SNP_A-2120958		0.017774444	0.071168568	A_A	116	-3.15	1.88
		0.017774444	0.071168568	A_B	77	-2.84	2.06
		0.017774444	0.071168568	B_B*	17	-1.11	2.13
		0.017774444	0.071168568	nonBB**	193	-3.03	1.96
SNP_A-2170121	C6	0.001634307	0.016887418	A_A	137	-2.14	1.85
		0.001634307	0.016887418	A_B**	53	-4.78	2.22
		0.001634307	0.016887418	B_B	14	-2.52	1.78
		0.001634307	0.016887418	nonAB*	151	-2.17	1.84
SNP_A-2283283	XKR4	0.002331952	0.018382642	A_A*	47	-0.95	1.47
		0.002331952	0.018382642	A_B	96	-3.20	2.06
		0.002331952	0.018382642	B_B	67	-3.62	1.99
		0.002331952	0.018382642	nonAA**	163	-3.37	2.03
SNP_A-4256833	MLCK	4.46659E-05	0.02283654	A_A	9	-3.58	1.63
		4.46659E-05	0.02283654	A_B*	64	-0.86	2.04
		4.46659E-05	0.02283654	B_B	137	-3.69	1.90
		4.46659E-05	0.02283654	nonAB**	146	-3.68	1.88
SNP_A-4258279	RRM1	0.012725795	0.202301911	A_A	2	-2.57	0.37
		0.012725795	0.202301911	A_B*	45	-1.09	1.96
		0.012725795	0.202301911	B_B	160	-3.34	1.85
		0.012725795	0.202301911	nonAB**	162	-3.33	1.84
SNP_A-1819750	CREG1	6.64422E-05	0.03950581	A_A	22	-5.35	1.71
		6.64422E-05	0.03950581	A_B*	119	-2.01	2.12
		6.64422E-05	0.03950581	B_B	46	-4.01	1.93
		6.64422E-05	0.03950581	nonAB**	68	-4.45	1.95
SNP_A-1860353	RAP1B	1.56517E-05	0.001522569	A_A**	5	-11.00	2.13
		1.56517E-05	0.001522569	A_B	35	-2.29	2.04
		1.56517E-05	0.001522569	B_B	169	-2.73	1.82
		1.56517E-05	0.001522569	nonAA*	204	-2.65	1.86
SNP_A-1975928	SLC2A9	0.017253052	0.094589657	A_A	150	-2.87	1.94
		0.017253052	0.094589657	A_B	48	-2.95	1.57
		0.017253052	0.094589657	B_B*	6	0.62	2.79
		0.017253052	0.094589657	nonBB**	198	-2.89	1.86
SNP_A-1987915	GPR126	3.12808E-05	0.022414357	A_A	27	-1.91	2.49
		3.12808E-05	0.022414357	A_B	97	-2.03	2.00
		3.12808E-05	0.022414357	B_B**	85	-4.28	1.93
		3.12808E-05	0.022414357	nonBB*	124	-2.00	2.11
SNP_A-2007721	LOC58486	0.000980061	0.00971944	A_A	1	0.51	
		0.000980061	0.00971944	A_B**	48	-4.73	1.93
		0.000980061	0.00971944	B_B	147	-2.33	1.95
		0.000980061	0.00971944	nonAB*	148	-2.31	1.95
SNP_A-2044214	HNT	0.040382222	0.031333432	A_A	86	-3.32	2.11
		0.040382222	0.031333432	A_B*	78	-2.16	1.94
		0.040382222	0.031333432	B_B	46	-3.05	1.76
		0.040382222	0.031333432	nonAB**	132	-3.22	1.99
SNP_A-2048427	NPAS3	0.002823078	0.039237616	A_A	9	-4.12	1.41
		0.002823078	0.039237616	A_B	56	-4.30	1.97
		0.002823078	0.039237616	B_B*	145	-2.27	1.96
		0.002823078	0.039237616	nonBB**	65	-4.28	1.89
SNP_A-2274533	LZTS1	0.000653736	0.01900311	A_A**	116	-3.67	2.03
		0.000653736	0.01900311	A_B	64	-1.52	1.84
		0.000653736	0.01900311	B_B	18	-1.16	2.05
		0.000653736	0.01900311	nonAA*	82	-1.44	1.88
SNP_A-2284243	GRIA4	7.94158E-05	0.010014455	A_A	63	-3.70	1.86
		7.94158E-05	0.010014455	A_B	99	-3.46	1.95
		7.94158E-05	0.010014455	B_B*	48	-0.52	1.95
		7.94158E-05	0.010014455	nonBB**	162	-3.55	1.91

TABLE 4-continued

SNPs associated with PANSS-N score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-4204396	CDH13	0.001334144	0.051404328	A_A	111	-3.22	1.90
		0.001334144	0.051404328	A_B	67	-3.12	1.93
		0.001334144	0.051404328	B_B*	15	1.62	2.13
		0.001334144	0.051404328	nonBB**	178	-3.18	1.91
SNP_A-4212785	PPP1R3B	5.46916E-05	0.047157777	A_A*	4	4.72	1.29
		5.46916E-05	0.047157777	A_B	67	-3.06	2.09
		5.46916E-05	0.047157777	B_B	124	-3.11	1.82
		5.46916E-05	0.047157777	nonAA**	191	-3.09	1.92
SNP_A-4230979	ASB3	4.20913E-05	0.004329523	A_A	26	-1.72	1.61
		4.20913E-05	0.004329523	A_B	98	-2.02	1.96
		4.20913E-05	0.004329523	B_B**	85	-4.23	2.01
		4.20913E-05	0.004329523	nonBB*	124	-1.96	1.89

¹SNPs are identified by their Affymetrix SNP nomenclature (SNP_A-)

²The gene name corresponds to the NCBI official symbol of the gene associated with the SNP as annotated by Affymetrix. Note that when a SNP is associated with more than one gene, the name of only the first gene in the annotation is listed. The SNP could be within or nearby the gene listed, or another gene in the same chromosomal region.

³p value of the MMRM analysis between the 2 genotype classes associated with lowest * or highest ** response to iloperidone treatment

⁴p value of the MMRM analysis between the iloperidone (Ilo) and placebo (Pbo) groups for the genotype class associated with the better response (**).

⁵The 2 genotypes classes used in the MMRM analyses are indicated as associated with lowest * or highest ** response to iloperidone treatment.

⁶The number of patients (N), the mean of change in PANSS-N (Mean), and the standard deviation of the mean (Std) shown here are derived from the MMRM analysis done within the group of iloperidone-treated patients.

TABLE 5

SNPs associated with PANSS-GP score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-1934663		6.70172E-06	0.133256964	A_A	15	-9.38	2.88
		6.70172E-06	0.133256964	A_B	58	-8.80	2.62
		6.70172E-06	0.133256964	B_B*	115	-3.07	3.33
		6.70172E-06	0.133256964	nonBB**	73	-8.92	2.67
SNP_A-1973093	KIAA0040	5.76184E-06	0.001577176	A_A	25	-6.40	2.49
		5.76184E-06	0.001577176	A_B*	76	-1.92	2.97
		5.76184E-06	0.001577176	B_B	105	-7.77	3.19
		5.76184E-06	0.001577176	nonAB**	130	-7.51	3.11
SNP_A-2070454	NKX2-5	0.001508458	0.00202546	A_A	44	-3.91	3.30
		0.001508458	0.00202546	A_B	94	-4.34	3.01
		0.001508458	0.00202546	B_B**	61	-8.12	2.94
		0.001508458	0.00202546	nonBB*	138	-4.20	3.10
SNP_A-2076797	NUDT9P1	3.36249E-05	0.17099973	A_A	57	-2.80	2.91
		3.36249E-05	0.17099973	A_B**	99	-8.23	2.98
		3.36249E-05	0.17099973	B_B	52	-2.42	2.96
		3.36249E-05	0.17099973	nonAB*	109	-2.62	2.93
SNP_A-2103099	HTR1A	0.000311502	4.11695E-05	A_A	38	-7.79	3.22
		0.000311502	4.11695E-05	A_B*	105	-3.42	3.15
		0.000311502	4.11695E-05	B_B	65	-6.80	2.76
		0.000311502	4.11695E-05	nonAB**	103	-7.16	2.96
SNP_A-2120958		0.000314352	0.020369025	A_A	116	-5.90	3.01
		0.000314352	0.020369025	A_B	77	-6.13	3.24
		0.000314352	0.020369025	B_B*	17	1.80	3.79
		0.000314352	0.020369025	nonBB**	193	-5.99	3.10
SNP_A-2170121	C6	3.69457E-05	0.002035176	A_A	137	-3.40	2.88
		3.69457E-05	0.002035176	A_B**	53	-10.21	2.69
		3.69457E-05	0.002035176	B_B	14	-5.25	3.23
		3.69457E-05	0.002035176	nonAB*	151	-3.57	2.95
SNP_A-2283283	XKR4	0.000210491	0.006474865	A_A*	47	-0.58	2.59
		0.000210491	0.006474865	A_B	96	-6.49	3.13
		0.000210491	0.006474865	B_B	67	-6.90	3.17
		0.000210491	0.006474865	nonAA**	163	-6.66	3.14
SNP_A-4256833	MLCK	0.001705341	0.016306876	A_A	9	-7.14	1.80
		0.001705341	0.016306876	A_B*	64	-2.62	3.36
		0.001705341	0.016306876	B_B	137	-6.45	3.14
		0.001705341	0.016306876	nonAB**	146	-6.49	3.08
SNP_A-4258279	RRM1	0.000310388	0.044200906	A_A	2	-4.64	6.48
		0.000310388	0.044200906	A_B*	45	-0.66	3.01
		0.000310388	0.044200906	B_B	160	-6.29	2.93
		0.000310388	0.044200906	nonAB**	162	-6.27	2.96
SNP_A-1819750	CREG1	0.074338855	0.398903123	A_A	22	-8.04	3.58
		0.074338855	0.398903123	A_B*	119	-4.58	3.12
		0.074338855	0.398903123	B_B	46	-6.81	3.21
		0.074338855	0.398903123	nonAB**	68	-7.21	3.35

TABLE 5-continued

SNPs associated with PANSS-GP score in iloperidone-treated patients							
SNP ¹	Gene ²	Iloperidone ³	Ilo vs. Pbo ⁴	Genotype ⁵	N ⁶	Mean ⁶	Std ⁶
SNP_A-1860353	RAP1B	0.002845774	0.012178225	A_A**	5	-17.20	2.97
		0.002845774	0.012178225	A_B	35	-5.17	2.99
		0.002845774	0.012178225	B_B	169	-4.96	2.88
		0.002845774	0.012178225	nonAA*	204	-5.00	2.90
SNP_A-1975928	SLC2A9	0.000154655	0.026316868	A_A	150	-5.82	3.09
		0.000154655	0.026316868	A_B	48	-5.39	2.99
		0.000154655	0.026316868	B_B*	6	9.62	4.95
		0.000154655	0.026316868	nonBB**	198	-5.72	3.06
SNP_A-1987915	GPR126	0.031457263	0.238695172	A_A	27	-4.63	3.20
		0.031457263	0.238695172	A_B	97	-4.28	3.18
		0.031457263	0.238695172	B_B**	85	-7.14	3.13
		0.031457263	0.238695172	nonBB*	124	-4.36	3.17
SNP_A-2007721	LOC58486	8.90971E-05	0.001841909	A_A	1	-2.52	
		8.90971E-05	0.001841909	A_B**	48	-10.51	3.30
		8.90971E-05	0.001841909	B_B	147	-3.91	2.61
		8.90971E-05	0.001841909	nonAB*	148	-3.90	2.60
SNP_A-2044214	HNT	0.015325757	0.040928723	A_A	86	-6.83	3.61
		0.015325757	0.040928723	A_B*	78	-3.34	2.53
		0.015325757	0.040928723	B_B	46	-5.68	3.04
		0.015325757	0.040928723	nonAB**	132	-6.43	3.46
SNP_A-2048427	NPAS3	6.59322E-05	0.03604452	A_A	9	-9.50	2.19
		6.59322E-05	0.03604452	A_B	56	-9.79	3.00
		6.59322E-05	0.03604452	B_B*	145	-3.44	2.83
		6.59322E-05	0.03604452	nonBB**	65	-9.75	2.89
SNP_A-2274533	LZTS1	0.000591957	0.012256756	A_A**	116	-7.04	2.98
		0.000591957	0.012256756	A_B	64	-2.16	3.09
		0.000591957	0.012256756	B_B	18	-2.33	2.36
		0.000591957	0.012256756	nonAA*	82	-2.20	2.94
SNP_A-2284243	GRIA4	0.000147192	0.00611101	A_A	63	-6.57	3.10
		0.000147192	0.00611101	A_B	99	-6.77	2.91
		0.000147192	0.00611101	B_B*	48	-0.77	3.12
		0.000147192	0.00611101	nonBB**	162	-6.69	2.98
SNP_A-4204396	CDH13	0.001744351	0.042910873	A_A	111	-5.87	3.06
		0.001744351	0.042910873	A_B	67	-5.99	2.98
		0.001744351	0.042910873	B_B*	15	1.39	3.87
		0.001744351	0.042910873	nonBB**	178	-5.91	3.03
SNP_A-4212785	PPP1R3B	4.17363E-06	0.040340673	A_A*	4	15.61	2.26
		4.17363E-06	0.040340673	A_B	67	-5.99	3.04
		4.17363E-06	0.040340673	B_B	124	-5.84	3.10
		4.17363E-06	0.040340673	nonAA**	191	-5.89	3.07
SNP_A-4230979	ASB3	6.83689E-06	0.000197511	A_A	26	-1.74	2.44
		6.83689E-06	0.000197511	A_B	98	-3.42	3.20
		6.83689E-06	0.000197511	B_B**	85	-8.85	3.05
		6.83689E-06	0.000197511	nonBB*	124	-3.07	3.12

¹SNPs are identified by their Affymetrix SNP nomenclature (SNP_A-)

²The gene name corresponds to the NCBI official symbol of the gene associated with the SNP as annotated by Affymetrix. Note that when a SNP is associated with more than one gene, the name of only the first gene in the annotation is listed. The SNP could be within or nearby the gene listed, or another gene in the same chromosomal region.

³p value of the MMRM analysis between the 2 genotype classes associated with lowest * or highest ** response to iloperidone treatment

⁴p value of the MMRM analysis between the iloperidone (Ilo) and placebo (Pbo) groups for the genotype class associated with the better response (**).

⁵The 2 genotypes classes used in the MMRM analyses are indicated as associated with lowest * or highest ** response to iloperidone treatment.

⁶The number of patients (N), the mean of change in PANSS-GP (Mean), and the standard deviation of the mean (Std) shown here are derived from the MMRM analysis done within the group of iloperidone-treated patients.

TABLE 6

Odds ratio, sensitivity, specificity, and predictive values of SNPs associated with change in PANSS-T in iloperidone-treated group													
SNP ¹	Gene ¹	Genotype ³	Delta-T $\geq -13^4$		Delta-T $< -13^4$		Odds Ratio	P	95% Confidence				
			-test	+test	-test	+test			Interval	Sensitivity	Specificity	PV ⁻⁵	PV ⁺⁶
SNP_A-2048427	NPAS3	non-GG	94	25	51	40	2.93	0.0005	1.596-5.388	0.44	0.79	0.65	0.62
SNP_A-2283283	XKR4	non-GG	35	84	12	79	2.82	0.0053	1.359-5.835	0.87	0.29	0.74	0.48
SNP_A-1973093	KIAA0040	non-AG	55	61	21	69	3.10	0.0003	1.671-5.744	0.77	0.47	0.72	0.53
SNP_A-2274533	GRIA4	non-TT	36	83	12	79	2.97	0.0035	1.431-6.148	0.87	0.30	0.75	0.49

TABLE 6-continued

Odds ratio, sensitivity, specificity, and predictive values of SNPs associated with change in PANSS-T in iloperidone-treated group													
SNP ¹	Gene ¹	Genotype ³	Delta-T ≥ -13 ⁴		Delta-T < -13 ⁴		Odds Ratio	P	95% Confidence	Sensitivity	Specificity	PV- ⁵	PV+ ⁶
			-test	+test	-test	+test			Interval				
SNP__A-2284243	LZTS1	AA	60	54	22	62	3.16	0.0002	1.715-5.832	0.74	0.53	0.73	0.53
SNP__A-2076797	NUDT9P1	GT	77	41	32	58	3.48	<0.0001	1.946-6.211	0.64	0.65	0.71	0.59

¹SNPs are identified by their Affymetrix SNP nomenclature (SNP_A-).

²The gene name corresponds to the NCBI official symbol of the gene associated with the SNP as annotated by Affymetrix. Note that when a SNP is associated with more than one gene, the name of only the first gene in the annotation is listed. The SNP could be within or nearby the gene listed, or another gene in the same chromosomal region.

³The genotype class shown here is the genotype class associated with better efficacy to iloperidone treatment.

⁴The number of patients with change in PANSS-T (Delta-T) above and below -13 is shown per genotype class. This threshold was chosen to calculate values of a test predicting ~20% improvement of the mean: the mean Delta-T value (-11) was calculated from the LOCF data within the iloperidone group and was chosen as the threshold for all calculations. The genetic test was defined as positive (+) for the genotype class specified ³ associated with better response, and negative (-) for all other genotypes.

⁵Predictive value negative (PV-).

⁶Predictive value positive (PV+).

Many SNPs are not known to contribute directly to a particular phenotype, but may be physically linked on the same chromosomal region to other functional polymorphisms which do contribute directly to a particular phenotype. Accordingly, in addition to, or instead of, determining the genotype of a SNP itself, methods according to the present invention may include direct sequencing and/or the characterization of an expression product of a gene with which the SNP is associated. Such expression products include mRNA, peptides, and proteins.

The present invention also includes the prediction of an individual's response to treatment with iloperidone based on one or more of the SNP loci above in combination with the individual's genotype or gene sequence at one or more additional genes or loci. For example, International Patent Application Publication No. WO2006039663, incorporated herein by reference, describes a method of treating an individual with a compound capable of inducing QT prolongation based on the individual's CYP2D6 genotype. Other genes associated with QT prolongation include KCNQ1 and CERKL. Another gene associated with iloperidone efficacy is CNTF. These genes are merely illustrative of the additional SNPs and/or genotypes that may be used. Other genotypes and/or gene sequences may similarly be used in combination with the SNP loci above.

In addition, while the study above involved the administration of iloperidone (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone), in some cases it may be advantageous to use iloperidone or an iloperidone metabolite preferentially in patients with certain genotypes as disclosed, e.g., in International Patent Application Publication No. WO2003054226, which is also incorporated herein by reference. Pharmaceutically-acceptable salts of iloperidone or iloperidone metabolites may also be used in the present invention.

Metabolites of iloperidone, e.g., P88 (also referred to as P-88-8891 or 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanol), are also useful in the present invention. See, e.g., International Patent Application Publication No. WO03020707, which is incorporated herein by reference. Other iloperidone metabolites include: 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2-hydroxyethanone; 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-_-methylbenzene methanol; 4-[3-[4-(6-fluoro-1,2-

20 benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-hydroxy-5-methoxy-_-methylbenzenemethanol; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-hydroxy-5-methoxyphenyl]ethanone; and 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2,5-dihydroxyphenyl]ethanone. See U.S. Pat. No. 5,364,866, and International Patent Application Publication Nos. WO9309276 and WO9511680, which are incorporated herein by reference.

30 Iloperidone, an iloperidone metabolite, and/or pharmaceutically-acceptable salts thereof may be administered in any number of forms, including, for example, tablets, capsules, oral solutions, intravenous solutions, intramuscular injectables, intradermal injectables, suppositories, patches, inhalants, and nasal sprays. Similarly, such compounds may be provided in immediate release formulations, extended release formulations, or long-term injectable formulations (e.g., 28 day depot formulations). In addition, methods according to the invention may include once-, twice-, or thrice-daily administrations.

The present invention includes other aspects in addition to those described above. For example, in the case that an individual's SNP genotype(s), DNA sequence, and/or expression products are not associated with greater iloperidone efficacy, the individual may be administered an increased dose of iloperidone, an iloperidone metabolite, and/or pharmaceutically-acceptable salts thereof. In addition, the individual may be administered more frequent doses than would an individual having a SNP genotype, DNA sequence, or expression product associated with greater iloperidone efficacy. Alternatively, the individual may be administered a compound other than iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt thereof.

55 In another aspect, the invention comprises a kit for determining a SNP genotype or DNA sequence or for characterizing an expression product according to a method described above.

In another aspect, the invention comprises a method of selecting individuals for a drug trial, wherein individuals are selected for inclusion based on a predicted response to treatment with iloperidone, an iloperidone metabolite, and/or a pharmaceutically-acceptable salt thereof using one or more of the SNPs above,

65 In another aspect, the invention comprises a method of analyzing results of a drug trial based on the patients' genotypes for one or more of the SNPs described herein.

In another aspect, the invention comprises screening and/or developing a composition having an increased or decreased efficacy in individuals of a particular genotype.

In another aspect, the invention includes a method of determining a genotype of an individual, the method including determining whether the individual possesses one or more SNPs above associated with greater iloperidone efficacy.

In yet another aspect, the invention includes a method of marketing iloperidone, an iloperidone metabolite, and/or pharmaceutically-acceptable salts thereof, the method including informing one or both of patients and pharmaceutical prescribers that individuals having one or more of the SNPs above associated with greater iloperidone efficacy are more likely to respond favorably to treatment with iloperidone, an iloperidone metabolite, and/or pharmaceutically-acceptable salts thereof.

The foregoing description of various aspects of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed, and modifications and variations are possible. Such modifications and variations that may be apparent to a person skilled in the art are intended to be included within the scope of the invention as defined by the accompanying claims.

What is claimed is:

1. A method of treating a human patient for one or more psychotic symptoms of using iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite, the method comprising:

determining, from a biological sample of the individual, the individual's genotype at the SNP_A-2048427 single nucleotide polymorphism (SNP) locus;
determining, from a biological sample of the individual, the individual's genotype at the SNP_A-2274533 SNP;
determining, from a biological sample of the individual, the individual's genotype at the SNP_A-2283283 SNP;
in the case that the individual's genotype is determined to be non-GG at the SNP_A-2048427 SNP, AA at the SNP_A-2274533 SNP, and non-GG at the SNP_A-2283283 SNP, predicting that treating the individual with a daily dosage of 24 mg of iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite will be efficacious and administering to the individual a daily dosage of 24 mg of iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite; and

in the case that the individual's genotype is determined to be GG at the SNP_A-2048427 SNP, non-AA at the SNP_A-2274533 SNP, or GG at the SNP_A-2283283 SNP, predicting that treating the individual with the daily dosage of 24 mg of iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite will be less efficacious than treating the individual with a daily dosage greater than 24 mg and administering to the individual a daily dosage greater than 24 mg of iloperidone, an iloperidone metabolite, or a pharmaceutically-acceptable salt of iloperidone or an iloperidone metabolite.

2. The method of claim 1, wherein efficacious treatment includes improvement in at least one of the following: Positive and Negative Syndrome Scale total score (PANNS-T), Positive and Negative Syndrome Scale positive (PANNS-P) subscale score, Positive and Negative Syndrome Scale negative (PANNS-N) subscale score, or Positive and Negative Syndrome Scale general psychopathology (PANNS-GP) subscale score.

3. The method of claim 1, wherein determining includes sequencing of a gene containing the SNP_A-2048427 SNP locus, the SNP_A-2274533 SNP locus, or the SNP_A-2283283 SNP locus.

4. The method of claim 1, wherein determining includes: characterizing, from the biological sample, an expression product of a gene containing the SNP_A-2048427 single nucleotide polymorphism (SNP) locus, the SNP_A-2274533 SNP locus, or the SNP_A-2283283 SNP locus; and

identifying the characterized expression product as associated with the non-GG genotype or the GG genotype at the SNP_A-2048427 SNP locus, with a non-AA genotype or the AA genotype at the SNP_A-2274533 SNP locus, and with the non-GG genotype or the GG genotype at the SNP_A-2283283 SNP locus.

5. A method of treating a psychotic symptom in a human individual, comprising:

determining, from a biological sample of the individual, that the individual's genotype at the SNP_A-2048427 single nucleotide polymorphism (SNP) locus is non-GG;

determining, from a biological sample of the individual, that the individual's genotype at the SNP_A-2274533 SNP is AA;

determining, from a biological sample of the individual, that the individual's genotype at the SNP_A-2283283 SNP is non-GG; and

administering to the individual a quantity of iloperidone.

6. The method of claim 5, wherein treating the psychotic symptom includes improving at least one of the following: Positive and Negative Syndrome Scale total score (PANNS-T), Positive and Negative Syndrome Scale positive (PANNS-P) subscale score, Positive and Negative Syndrome Scale negative (PANNS-N) subscale score, or Positive and Negative Syndrome Scale general psychopathology (PANNS-GP) subscale score.

7. The method of claim 5, wherein determining includes sequencing of a gene containing the SNP_A-2048427 SNP locus, the SNP_A-2274533 SNP locus, or the SNP_A-2283283 SNP locus.

8. The method of claim 5, wherein determining includes: characterizing an expression product of a gene containing the SNP_A-2048427 single nucleotide polymorphism (SNP) locus, the SNP_A-2274533 SNP locus, or the SNP_A-2283283 SNP locus; and

identifying the characterized expression product as associated with the non-GG genotype or the GG genotype at the SNP_A-2048427 SNP locus, with a non-AA genotype or the AA genotype at the SNP_A-2274533 SNP locus, and with the non-GG genotype or the GG genotype at the SNP_A-2283283 SNP locus.

9. The method of claim 5, wherein the quantity of iloperidone is a daily dosage of 24 mg.

10. A method of treating a psychotic symptom in a human individual, comprising:

determining that the individual's genotype at the SNP_A-2048427 SNP locus is GG, that the individual's genotype at the SNP_A-2274533 SNP locus is non-AA, or that the individual's genotype at the SNP_A-2283283 SNP locus is GG; and

administering to the individual a quantity of iloperidone greater than would be administered to an individual having a non-GG genotype at the SNP_A-2048427 SNP locus an AA genotype at the SNP_A-2274533 SNP locus, or a non-GG genotype at the SNP_A-2283283 SNP locus.

11. The method of claim 10, wherein treating the psychotic symptom includes improving at least one of the following: Positive and Negative Syndrome Scale total score (PANNS-T), Positive and Negative Syndrome Scale positive (PANNS-P) subscale score, Positive and Negative Syndrome Scale 5 negative (PANNS-N) subscale score, or Positive and Negative Syndrome Scale general psychopathology (PANNS-GP) subscale score.

12. The method of claim 10, wherein determining includes sequencing of a gene containing the SNP_A-2048427 SNP 10 locus, the SNP_A-2274533 SNP locus, or the SNP_A-2283283 SNP locus.

13. The method of claim 10, wherein determining includes: characterizing an expression product of a gene containing the SNP_A-2048427 single nucleotide polymorphism 15 (SNP) locus, the SNP_A-2274533 SNP locus, or the SNP_A-2283283 SNP locus; and identifying the characterized expression product as associated with the non-GG genotype or the GG genotype at the SNP_A-2048427 SNP locus, with a non-AA geno- 20 type or the AA genotype at the SNP_A-2274533 SNP locus, and with the non-GG genotype or the GG genotype at the SNP_A-2283283 SNP locus.

* * * * *